DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 3 0 1999

Dr. John L. Pfenninger
The Medical Procedures Center, P.C.
4909 Hedgewood Drive
Midland, MI 48640

RE: 97M-0254/PRC3

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Dear Dr. Pfenninger:

This letter is in response to your July 28, 1997 petition requesting administrative review of FDA's decision to approve the Premarket Approval Application (PMA) for the ThinPrep 2000 System manufactured by Cytyc Corporation. In your petition you requested that an advisory committee of experts be convened, as provided in section 5 15(g)(2) of the Federal Food, Drug, and Cosmetic Act (the act), to conduct an independent study of the data and information that led to FDA's May 20, 1996 approval of the ThinPrep PMA (P950039) and its February 25, 1997 approval of Supplement P950039/SO05 permitting the sponsor to make certain claims about the performance of the device. FDA apologizes for not answering your petition sooner.

In addition to your petition, FDA received six additional petitions (Docket # 97M-0254/PRCl, 2, 4-6) requesting that an advisory committee of experts be convened to review FDA's approval of this device. Because the issues raised by you and the other petitioners are of the same general nature, and because there is considerable overlap on specific points, FDA's response to each petitioner addresses the issues raised in all seven petitions.

None of the petitioners seeks reversal of the PMA approval. Rather, the petitioners request that the word "screening" be eliminated from the description of the device's intended use and that the intended use of the device be changed from "intended as a replacement for the conventional method of Pap smear preparation "to intended as adjunct to conventionally prepared Pap smears." The petitioners also request that the labeling of the device be modified to reflect these changes.

FDA has considered carefully the information provided in your and the other petitions received. The agency has determined that the objections raised in the petitions do not raise genuine and substantial issues of fact sufficient to justify convening an advisory committee of experts. In addition, the petitions do not demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered.

Standard for Convening an Advisory Committee of Experts

Section 515 (d)(3) of the act provides that any interested person may obtain review, in accordance with section 5 15(g)(1) (through a formal evidentiary hearing) or (g)(2) (by an advisory committee of experts), of an order by the Secretary approving a PMA. All seven petitioners challenging the approval of the ThinPrep device requested review by an advisory committee of experts. Some petitioners requested that the order be reviewed by the same panel that considered the premarket approval application. However, as provided in section 515(g)(2)(B), the advisory committee of experts to be convened to review a challenge to a PMA approval order may not be a panel under section 513.

The Federal Register notice announcing the approval of this device (62 F.R. 35212 (June 30,1997)) stated that a person seeking review of the PMA decision should submit a petition for reconsideration in

97M-0254

PDN3

2. ***The intended use statement should not mention diagnostic categories because Pap smear reading does not have the same meaning as detection/non-detection of cervical pathology by colposcopy and biopsy.***

The labeling of the ThinPrep processor states that the device "is intended as a replacement for the conventional Pap smear preparation for use in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low- grade Squamous Intraepithelial Lesions, High-grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnosis[1]." It is clear from this intended use statement that the ThinPrep processor is simply a different method of preparing Pap smear slides for reading. Like the conventional method of Pap smear slide preparation it may replace, and as specifically stated in the intended use statement, the device is for use in screening for abnormal cells. The labeling does not state or suggest that the device is intended to be used for diagnosing disease. The Bethesda System diagnostic categories identified in the label of the ThinPrep device inform clinicians and laboratorians what categories can be successfully identified using the ThinPrep processor method of slide preparation.

The petitioners have submitted no data or information establishing an issue of fact as to whether the intended use statement is inaccurate. Rather, it appears that the petitioners have misconstrued the intended use statement. Both the agency and the panel members to whom the application was referred carefully considered the wording of the intended use statement, including identification of the Bethesda System categories, before approving the device. Consequently, the agency concludes that this objection does not raise a genuine issue of material fact for resolution by an advisory committee of experts, nor does it demonstrate that relevant information or views contained in the administrative record were not adequately or not previously considered.

3. ***The standard of approval of the ThinPrep PMA was comparison to Pap smear and not to histologically confirmed cases and, therefore, the true sensitivity of the device has not been established***

FDA agrees with the petitioners that approval of the ThinPrep PMA was based on a comparison of Pap smear readings conducted on ThinPrep prepared slides with Pap smear readings conducted on conventionally prepared slides, without histologic confirmation of results. According to the study design, confirmatory cytologic readings and discrepancy resolution determined outcome. A total of 1931 slides positive by either or both preparation methods, plus five percent of concordant negative slides were selected for an independent pathologist's masked review. Consistent with this approach, the performance characteristics of the ThinPrep *2000* System are not reported in terms of sensitivity and specificity. In fact, the ThinPrep label specifically states that the true sensitivity of the device has not been established.

There is no factual dispute concerning whether the true sensitivity of the device has been established. FDA does not require that the true sensitivity of every in vitro diagnostic device be established before it may conclude that there is reasonable assurance of its safety and effectiveness sufficient to support approval.

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[1] **The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses was developed by the National Cancer Institute to provide uniform diagnostic terminology that would facilitate communication between the laboratory and the clinician. In the Bethesda System the epithelial squamous cell abnormalities are classified as follows: atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesion (LSIL) encompassing human papilloma virus/mild dysplasia/cervical intraepithelial lesion (CIN) 1; highgrade squamous intraepithelial lesion (HSIL) encompassing moderate dysplasia, severe dysplasia, and carcinoma in situ/CIN 2 and CIN 3; squamous cell carcinoma.**

Therefore, the fact that the true sensitivity was not established is not material to and, therefore, would not change the agency's decision to approve the device for its intended use. Both the agency and the panel members who reviewed the PMA considered whether this comparison of the readings was sufficient to support approval of the device. In fact, FDA specifically asked the panel members whether they believed that the reading of the refereed pathologist was a sufficient end-point on which to base approval. Both FDA and the panel members who reviewed the PMA concluded that the comparison of the readings was acceptable. This objection, therefore, does not demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered. Consequently, FDA concludes that review by an advisory committee of experts is not justified based on this objection.

4. ***Because the clinical testing of the ThinPrep was conducted under different guidelines than those applicable to similarly indicated in vivo technologies, as described in recently published draft FDA guidance, the device should not have been approved for its intended use.***

The ThinPrep processor was tested in accordance with FDA guidelines for in vitro devices. As the petitioners state, the clinical testing of the ThinPrep processor was conducted under different guidelines than those proposed for devices utilizing in vivo technologies. However, the ThinPrep processor is an in vitro device and the draft guidelines referred to in the petitions, "In Vivo Devices for the Detection of Cervical Cancer and its Precursors: Submission Guidance for an IDE", apply to in vivo, not in vitro, devices. Moreover, the guidelines apply to in vivo devices intended for the direct detection of cancer lesions in the cervix. These in vivo devices, when indicated for primary screening of cervical cancer, are indicated as an alternative to the cytology smear itself. The guidelines do not apply to in vitro devices intended for use in cervical cancer screening. The ThinPrep processor is an in vitro device intended for use in cervical cancer screening. It is not intended to be used as an alternative to the cytology smear itself. The guidelines do not apply to in vitro devices intended for use in cervical cancer screening. Consequently, for several reasons, the guidelines cited by the petitioners do not apply to the ThinPrep device.

The agency concludes that this objection raises no genuine issue of material fact for resolution by an advisory committee of experts. Because the guidelines do not apply to devices like the ThinPrep processor, the fact that the study did not comply with the guidelines is immaterial to and, consequently, can have no effect on, the approval order. There is simply no live, factual controversy presented in this objection about which an advisory committee could conduct a meaningful review. Similarly, the objection does not demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered.

5. ***Because there were no biopsy data, the claimed increase in detection of low-grade squamous intraepithelial and more severe lesions (LSIL+) by ThinPrep prepared slides as compared to conventionally prepared slides could be due to an increase in false positive results. Also, it is unclear which lesion category could be detected more effectively by ThinPrep prepared slides than by conventionally prepared Pap smear slid-***

The conclusion of the ThinPrep clinical study was that the ThinPrep 2000 system was significantly more effective than the conventional Pap smear for the detection of low-grade squamous intraepithelial and more severe lesions (LSIL+). When all cytologic categories from LSIL to cancer cells were grouped in one category (LSIL+), there was a statistically significant increase in detection of LSIL+ for the ThinPrep prepared slides when compared to the conventionally prepared Pap smears. This increase in detection was observed both when the site pathologists read the slides, and when the independent pathologist reviewed the discrepant slides. (The aggregation of LSIL, HSIL, and carcinoma categories into one group for statistical analysis was acceptable to FDA when reviewing ThinPrep's clinical trial because, from the clinical point of

view, the principal function of the Pap smear is to identify patients with abnormalities who need follow-up). As a point of clarification, the ThinPrep 2000 System approval was based on equivalent or better performance in each category and not on an increase in detection overall.

The petitioners suggest that the cell morphology in ThinPrep prepared slides is distorted to the point of leading to false positive Pap smear readings. It is true that there are differences in cell morphology between the ThinPrep and the conventionally prepared slides. However, as stated in the ThinPrep label, "Evaluation of the microscope slide produced with the ThinPrep 2000 System should be performed only by cytotechnologists and pathologists who have been trained to evaluate ThinPrep prepared slides by Cytyc Corporation or by organizations or individuals designated by Cytyc Corporation." Properly trained professionals will recognize the subtle differences in cell morphology that exist between the two methods of slide preparation. The ThinPrep clinical study shows no evidence that the rate of false positive results following the use of ThinPrep slides is higher than the one associated with readings of conventionally prepared Pap smear slides. To the contrary, published clinical studies submitted by either the petitioners or by Cytyc in its response to the petitions, which included cervical biopsy results, do not support the petitioners' objection that there may have been an excess of false positive results when using ThinPrep.

Biopsy data from two studies conducted at the Pap Smear Evaluation Center at Brigham and Women's Hospital (one of ThinPrep study sites) were submitted. The first study was "Colposcopically Directed Biopsies Provide a Basis for Comparing the Accuracy of ThinPrep and Papanicolaou Smears", published by Dr. Ellen E. Sheets and colleagues in the March 1995 issue of the Journal of Gynecologic Techniques. This study was submitted on December 5, 1997 as an attachment to comments of Cytyc Corporation on the petitions for reconsideration; it was not part of the PMA. The study by Dr. Sheets included 786 consecutive patients and 782 pairs of Pap smears and ThiiPrep slides; colposcopy biopsies were taken from 445 patients. The two cytologic diagnoses agreed exactly in 89.8% of the cases. When histologic diagnosis was used to classify the discordant cases into two groups, negative/atypical and LSIL/HSIL/carcinoma, the correlation between the two cytologic diagnoses showed that the ThinPrep method was significantly more sensitive than the conventional Pap preparation method for the detection of cervical lesions. The specificity of both methods was equivalent. For the 159 cases that were positive histologically (LSIL/HSIL/carcinoma), both the Pap smear and the ThinPrep slide showed LSIL/HSIL/carcinoma in 103 cases and no neoplasia or its precursor lesions in 38 cases. Fourteen LSIL/HSIL/carcinoma cases were diagnosed solely on the ThinPrep slide and 4 cases of LSIL/HSIL/carcinoma were diagnosed solely on the Pap smear. When the histology was negative, there was no difference between the two preparation methods, The study by Dr. Sheets indicates that the increase in detection of low-grade squamous intraepithelial and more severe lesions by ThinPrep prepared slides as compared to conventionally prepared slides is not due to an increase of false positive results.

The second study was "Colposcopically Directed Biopsy as a Basis for Comparing the Diagnostic Accuracy of the ThinPrep and Papanicolaou Smear Methods" published by Dr. Kenneth Lee and colleagues (Dr. Sheets was one of the co-authors) in abstract format on the September-October 1996 issue of the *Acts Cytologica* (publication subsequent to ThinPrep's approval). This study, which was submitted by one of the petitioners, included 971 patients, 171 of whom had follow-up biopsy. The results showed an 18°/0 increase in detection of cervical abnormalities (ASCUS and higher) with ThinPrep slides. Comparison of the biopsy diagnosis with both ThinPrep and conventionally prepared Pap smear slides showed that the two cytologic methods detected a similar numbers of abnormalities. The study by Dr. Lee indicates that, for ASCUS and higher lesions (as opposed to LSIL and more severe lesions), both methods of Pap smear slide preparation detect the same number of abnormalities.

Because the information the petitioners submitted does not support their suggestion that the increase in detection of low-grade squamous intraepithelial and more severe lesions as compared to conventionally prepared slides may have been attributable to an increase in false positive results, the petitioners have submitted no data and information to support resolution of this issue in the manner they seek. Consequently, this objection raises no genuine issue of material fact warranting review by an advisory committee of experts. Moreover, when considering the PMA supplement (Supplement number 5), the agency considered whether the *increase* in detection might be due to an excess of false positive results and concluded that it was not. This objection, then, does not demonstrate that relevant information or views contained in the administrative record were not adequately or not previously considered. The agency concludes, therefore, that review by an advisory committee of experts is not justified based on this objection.

6. The ***petitioners object that no advisory panel meeting was held to review the ThinPrep PMA.***

As amended by the Safe Medical Devices Act of 1990 (SMDA), section 5 15(c)(2) of the act provides that, unless the sponsor of a PMA requests that its application be referred to a panel, FDA has discretion to determine whether to refer a particular PMA to an advisory panel. The agency is not required to refer every PMA to a panel for its review or to convene a meeting of the advisory panel for every PMA.

The PMA for a previous version of the ThinPrep processor (P920009) was discussed by the Hematology and Pathology Devices Advisory Panel on June 7, 1993 (the panel recommendation was approvable with conditions). This submission was subsequently withdrawn by Cytyc Corporation. The PMA that led to the approval of the ThinPrep device was reviewed as a homework assignment by four panel members (three cytopathologists and one gynecologic oncologist). A meeting of the advisory panel was not convened because the agency determined that there were no safety and effectiveness issues for which it was necessary to convene a panel meeting.

This objection raises no question of fact for resolution by an advisory committee of experts. Rather, it represents a disagreement with the agency's policy decision not to convene a panel meeting to review a particular PMA. The objection does not demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered. The agency concludes, therefore, that review by an advisory committee of experts is not justified based on this objection.

7. The ***Cytyc clinical study failed to simulate the 200 slides/day allowable limit. The device label should clearly disclose to clinicians the screening rates used by cytotechnologists in the clinical trial.***

According to regulations issued by the Health Care Financing Administration (HCFA), each laboratory is responsible for ensuring that individuals engaged in the evaluation of cytology preparations by a nonautomated microscopic technique examine no more than 200 slides in a 24-hour period. See 42 C.F.R. 493.1257 (b)(l). The regulations further state that, 'This limit represents an absolute maximum number of slides and is not to be employed as a performance target for each individual." (Id.). The actual rate of slide examination is to be determined by the supervisor at each individual laboratory. 42 C.F.R. 493.1257(c).

The examinations of both ThinPrep and conventionally prepared slides in the ThinPrep clinical study were conducted to reflect routine workload, i.e., the study was conducted mirroring the intended routine daily use of the device following approval. Cytyc makes no claim that an individual can examine 200 ThinPrep slides per day.

FDA agrees that the ThinPrep clinical study failed to simulate the 200 slides/day allowable limit. Thus, there is no factual dispute presented by this objection. Rather, the petitioners have raised a question of policy with respect to whether the labeling of in vitro devices generally should disclose the screening rates used in their clinical trials. As stated previously, the 200 slide per day limit is established by HCFA and applies, not to devices, but to the laboratories in which they are used. Unless manufacturers wish to make claims regarding the number of slides that can be read per day with its device, FDA believes it is not necessary to require that the labeling of in vitro devices disclose the screening rates used in their clinical trials. Because this is a question of administrative policy rather than fact, FDA has concluded that review by an advisory committee of experts is not justified based on this objection. The objection also fails to demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered.

8. ***Cytyc failed to include enough cancer cases to allow determination of ThinPrep's ability to correctly classify cancer cases and of those cases presented in the clinical study, ThinPrep incorrectly classified severaL***

Because of the low prevalence of cervical cancer and the inclusion in the study of populations with low prevalence of previously abnormal Pap smears, there were only four cases read as cancer in the ThinPrep clinical trial. Consequently, Cytyc conducted additional clinical and nonclinical studies to support the claim that the ThinPrep processor is effective for preparing slides that can detect cervical cancer. Cytyc submitted filtration studies showing that cancer cells were not filtered out during the ThinPrep process and that no particular kind of cell was lost disproportionately. In addition, Cytyc submitted a retrospective clinical study with a total of 48 samples that included 23 cervical cancer cases. In this study, 19 of 23 cancer cases were classified on the conventional Pap smear slides, and 17 of 23 on the ThinPrep slides. Based on the filtration studies it was concluded that the discrepancies observed were due, at least in part, to the nature of the "split sample" collection method that slightly favors the conventional Pap smear. This study demonstrated that the ThinPrep prepared slides contained sufficient numbers of cancer cells for detection.

Contrary to the petitioners' assertion, ThinPrep reading classified three of the four clinical study cancer cases correctly (a case of adenocarcinoma was read as AGUS), while the conventional Pap Smear reading incorrect y classified two of the four cases (two high-grade intraepithelial lesions were read as squamous cell carcinoma). Thus, in the clinical study the ThinPrep prepared slides led to more accurate readings than did the conventionally prepared Pap smear slides. Moreover, all of the abnormal Pap smears prepared using the ThinPrep device led to diagnostic follow-up, consistent with the intended use of the device.[2]

There is no factual disagreement between FDA and the petitioners with respect to what the ThinPrep studies showed, Rather, the petitioners disagree with the agency's conclusion that the PMA contained enough data from which conclusions regarding the ability of the device to correctly classify cancer cases could be drawn. Yet, the petitioners have submitted no information or data that, if accurate, would support their conclusion. This objection, then, consists of unsupported conclusions regarding a question of law or of administrative policy about whether the PMA contained valid scientific evidence sufficient to support approval of the device for its intended use. Both the agency and the panel members who reviewed the PMA considered whether the PMA contained a sufficient number of cancer cases from which conclusions regarding the ability of the device to correctly classify cancer cases could be drawn and determined that it

[2] As stated previously, Thin Prep, like conventionally prepared slides, is a screening tool intended to identify patients for follow-up. It is intended to identify abnormality. Follow-up is then necessary to determine the exact degree of abnormality.

did. The objection does not demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered. Accordingly, FDA has concluded that review by an advisory committee of experts is not justified based on this objection.

9. ***Cytyc failed to adequately test the device's ability to detect endocervical adenocarcinoma.***

During the clinical study, 20 cases of AGUS (atypical glandular cells of undetermined significance) were detected on slides prepared with ThinPrep while 8 cases were detected with conventionally prepared slides. However, because the ThinPrep slides had no endocervical components in 6.4% more cases than the conventionally prepared Pap smear slides, Cytyc then conducted two additional studies in order to determine whether slides prepared with ThinPrep were equivalent to conventionally prepared slides with respect to the presence of endow-vied components. These studies were performed with samples rinsed directly into the PreservCyt vials (simulating the actual intended use of the device) instead of using the split sample technique utilized in the clinical trial. One of the studies was a feasibility study (299 cases) which compared ThinPrep sample adequacy with historical and published controls; the other study (484 cases) assessed sample adequacy by comparing the performance of ThinPrep slides to published specimen adequacy rates on conventional Pap smears, and to split sample ThinPrep slides. The outcome of these studies was measured by the number of slides determined to be satisfactory but limited by no endocervical component. Both direct-to-vial studies showed no difference between ThinPrep and conventionally prepared Pap smear slides in the percentage of satisfactory-but-limited-by no-endocervical-component slides when the ThinPrep method was used as intended, i.e., with the sample placed directly in the vial.

In support of this objection, the petitioners submitted a published article by a doctor who had studied both ThinPrep and conventional Pap smear in a high-risk population. Yet, the author of the article concluded that, with respect to its ability to detect malignancy, the overall correlation between ThinPrep and conventional Pap smear is excellent. Thus, the information on which the petitioners rely to support their objection, in fact, supports the agency's conclusion. Consequently, the petitioners have submitted no data or information that, if proven true, would support their objection and warrant a change in the approval of the device. Both the agency and the panel members who reviewed the PMA considered whether Cytyc had adequately tested the ability of the device to detect endocervical adenocarcinoma and determined that it had. Consequently, the objection does not demonstrate that relevant information or views contained in the administrative record were not previously or not adequatel y considered. FDA has concluded, therefore, that review by an advisory committee of experts is not justified by this objection.

10. ***The ThinPrep clinical study failed to meet standards set by the Hematology and Pathology Advisory Panel at its November 96 (actually September 27, 1996) meeting (for Neopath's AutoPap device), the Intersociety Working Group for Cytology Technologies, and the College of American Pathologists (CAP)***

The recommendations made by the Hematology and Pathology Advisory Panel at its September 27, 1996 meeting were directed specifically to the AutoPap device, an automated primary screening (reading) device manufactured by Neopath. The recommendations were not intended to apply to slide preparation devices, like the ThinPrep processor. Rather, they applied to a primary screening instrument, i.e., a device intended to triage gynecologic cytology slides for identification of malignant or premalignant disease. Moreover, these recommendations were set after the approval of the ThinPrep device. The Proposed Guidelines for Primary Screening Instruments for Gynecologic Cytology developed by the Intersociety Working Group for Cytology Technologies published in May/June 1997 are also directed to primary screening devices. The CAP standards referred to by the petitioners are recommendations made by CAP to FDA in a letter dated August 28, 1996 with respect to issues to be considered in developing review standards for automated

primary screening instruments for gynecologic specimens, that is, for devices providing the cytologic reading.

There is no factual dispute with respect to whether the ThinPrep clinical study met the recommendations and standards referred to in the objection. Moreover, because the recommendations and standards did not apply to this type of device, the fact that the study did not follow them is not material to, and can have no impact on, the agency's decision to approve the device for its intended use. Consequently, the objection does not raise a genuine issue of material fact. In addition, the objection does not demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered. Accordingly, the agency has concluded that review by an advisory committee of experts is not justified based on this objection.

Conclusion

FDA has evaluated the objections raised in the petitions submitted regarding the approval of the ThinPrep 2000. FDA has concluded that none of the objections raise genuine and substantial issues of material fact for review by an advisory committee of experts. Rather, some objections represent disagreements with the agency's conclusion that the PMA contained valid scientific evidence sufficient to support approval of the device for its stated intended use. These disagreements do not raise issues of fact, but rather questions of law or of administrative policy. Other objections raise issues not material to the agency's decision to approve the device for its intended use. None of the objections demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered. The agency has concluded that it would serve no useful purpose to convene an advisory committee of experts to consider the objections raised in the petitions. Therefore, your request for administrative review to reconsider FDA's approval of the ThinPrep 2000 System PMA is denied.

Sincerely,

William K. Hubbard
Acting Deputy Commissioner for Policy

cc: Kate C. Beardsley
Counsel for Cytyc Corporation